REMARKS

Claims 25-28 and 30-43 are pending in this application. The examiner has withdrawn claims 30-37 from further consideration. Claim 25 is cancelled without prejudice or disclaimer. Claims 26-28 are amended for clarity and to recite specific structural features of the antagonist. Claim 26 is amended to an independent form including features from the cancelled claim 25. Claims 38-43 are new.

New claims 38-41 are added to focus on the features of the antagonist defined by SEQ ID NO:10. Claims 38 and 41 are added to define the integrins recited in claim 26. Support for the subject matters recited in claims 38 and 41 can be found throughout the specification, for example, see page 19, line 12, page 20, line 32, page 21, line 10 and page 22, line 6 of the application as filed. Claims 39 and 40 specify the structural features relating to SEQ ID NO:10. Support for the subject matters recited in claims 39 and 40 also can be found throughout the specification, for example, see previously presented claim 26, page 20, line 19, and page 24, line 24. Support for the new claims 42 and 43 can be found in the specification, see for example, page 6, lines 1-16. Therefore, no new matter is introduced.

Amended and the new claims are directed to antagonists having specific structural features, rather than antagonists which can bind to a ligand for an epitope having certain structural features. Although SEQ ID NO:9 was elected for consideration during examination, applicants request rejoinder of the new claims in view of the arguments presented herein in favor of claim 26.

The office action is discussed below.

Withdrawn and New Claims:

Applicants note that claims 30-37 remains withdrawn. Applicants respectfully request examination of these claims and the newly added claims 38-43 since each ultimately depends from claim 26 or relate to the same special technical feature, for example, ICAM-4 or an antagonist derived thereof. Examination of these claims does not seem to present an undue burden on the examiner.

Enablement/ Written Description Rejection:

On pages 2-5 of the Office Action, the examiner maintains the rejection of claims 25-28 under 35 U.S.C. 112, first paragraph, allegedly as being non-enabling. The examiner states that in view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Applicants respectfully disagree with the examiner and submit that the claims are enabled by the Examples included in the specification, which are further supported by the knowledge of the person skilled in the art (see Kaul *et al.*, *Am. J. Physiol. Cell Physiol.* (2006) 291: C922-C930, a copy of which is enclosed). An enablement rejection only can be supported when the experimentation needed to practice the claimed invention is considered 'undue' by the field. Accordingly, in making a rejection the Examiner must distinguish between routine work and undue experimentation. *See* MPEP § 2164.06 (Rev. 1, February 2000; also see Rev. 6. September 2007 at 2100-201).

In the present situation, Examples are included in the specification that enable one skiled in the art obtain the claimed antagonists. In fact, based on the instant disclosure, screening would be practiced by the skilled person in order to obtain the claimed antagonists. As explained above, the skilled person is provided with a screening approach by applicants' specification. In similar circumstances, the Federal Circuit has considered applications enabling where screening was required. *See In re Wands,* 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (holding an application enabled where there was "considerable direction and guidance" in the specification, "a high level of skill in the art," and the "methods needed to practice the invention were well known."); MPEP § 2164.01(a) (Rev. 6, September 2007). These factors inure to applicants' benefit regarding the screening aspects of the present invention.

Applicants also refer that screening of mutants and constructs is expected in biotechnology, and therefore it cannot amount to undue experimentation. Rather, screening is a routine task that is considered part of the normal practice in this field. *See Falkner v. Inglis,* 448 F.3d 1357, 1365 (Fed. Cir. 2006); *In re Wands,* 858 F.2d 731, 740

Fed. Cir. 1988); *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384 (Fed. Cir. 1986); *Ex parte Mark*, 12 USPQ2d 1904, 1907 (Bd. Pat. App. Int. 1989).

Applicants further refer that antagonist residues and other, less identical, sequences can be made in view of the teachings of Examples 1-3 of the specification (see for example, pages 16-23 and pages 23-27 for sequences and amino acid residues), disclosures of Figures 1-20 and the description on pages 8-16). Thus, such less identical sequences need not be disclosed in a specification. *See Falkner v. Inglis,* 448 F.3d 1357, 1365 (Fed. Cir. 2006). Moreover, the immunogenicity of such less identical sequences can be readily screened in view of the instant specification, and such screening is an expected part of the practice of biotechnology. *See In re Wands,* 858 F.2d 731, 740 Fed. Cir. 1988); *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384 (Fed. Cir. 1986).

Claim 25 is cancelled without prejudice or disclaimer. Claims 26-28 are amended for clarity and to recite specific structural features of the antagonist. Claims 27 and 28 are directed to focus on the features of the antagonist as defined by SEQ ID NO:9. Since the currently amended claims are directed to antagonists having specific structural features, rather than antagonists which can bind to a ligand for an epitope having certain structural features, applicants submit that many of the examiner's comments are now moot.

Applicants provide the following clarifications and arguments in order to assist the examiner understanding that the claimed inventions are enabled:

The examiner appears to suggest that, because not all of the amino acid positions are specified in the claims for the antagonist peptide, the skilled person is placed under an undue burden to determine whether a particular compound is an antagonist or not. The examiner pointed to Huang (2000) as evidence of such difficulty. The relevant passage of Huang (first paragraph of page 202, sentence 6 onwards) lists the many steps which the skilled person must go through in a drug design program. However, all of the steps are, in light of current scientific knowledge, wholly routine to the skilled person. In the final sentence of this passage, Huang comments that production of such small molecule drugs has an advantageously low cost compared to development of other drug candidates, suggesting that, in fact, the procedure to go through is not especially onerous.

In the subsequent paragraph, Huang goes on to comment that "...interactions between proteins involve large and relatively flat surface areas with many contact sites ... As such, it is often believed that the design of small molecules to disrupt such complex and diffuse protein-protein interactions would appear to be a daunting task...." However, in the present context, the claims provide a clear indication of amino acid residues to be included in the antagonist and the specification indicates the important regions and specific residues of ICAM-4 which may be used to define the epitope for a ligand. In addition, examples of antagonists of such a ligand are provided, along with means of determining whether a candidate indeed acts as an antagonist (this being the work that the applicants themselves carried out). The specification sets out clear instructions for how to identify possible antagonists (see Example 1) and how to determine whether the antagonists indeed prevent ligand binding to ICAM-4 (see Examples 1 & 2). Therefore, according to Huang's analysis, the "daunting" nature of small molecule design is very much reduced. The work might still be time-consuming, but it is not onerous nor unexpected, and does not require the utilization of inventive skill in view of the teachings of the specification. In this context, applicants refer to the dictates of the MPEP that:

> "The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). .....Time and difficulty of experiments are not determinative if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404."
> *See* MPEP § 2164.06 (Rev. 6, September 2007 at 2100-201).

In relation to the examiner's comments regarding the publications by Kuntz and by Miller, since the specification provides clear details of important binding regions and residues of ICAM-4, the skilled person is provided with sufficient information to obtain the antagonist of the invention. In relation to the claims as amended, the required structural features of the antagonist are provided and examples of antagonists which fall within this definition (SEQ ID NOs: 9 & 10) have been provided and characterized. Although experimentation may be required to identify further antagonists, no inventive skill is needed, since the skilled person needs only to follow the instructions provided in the

specification to determine whether a given small peptide falls within the scope of the claims. As clarified above, other, less identical, sequences can be made in view of the teachings of the applicants' specification (see for example, pages 16-27 for sequences and amino acid residues, Figures 1-20, and the description on pages 8-16). Thus, such less identical sequences need not be disclosed in a specification. *See Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006). Moreover, the immunogenicity of such less identical sequences (small peptides *per se*) can be readily screened in view of the instant specification, and such screening is an expected part of the practice of biotechnology. *See In re Wands,* 858 F.2d 731, 740 Fed. Cir. 1988); *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384 (Fed. Cir. 1986).

The examiner had objected to claims 27-28 because SEQ ID NO:9 contains 9 amino acids and, in the case of claim 27, not all of these amino acids were defined. The examiner asserted that the term "includes" in claim 27 was open-ended. Applicants do not agree with this, in the context of the use of the word in the claim; however, to aid the examiner's understanding the language of the claim has been amended with a view to improving its clarity. The claim is dependent on claim 26 which requires that the antagonist "consists essentially of" 3 to 9 amino acids, with claims 27 and 39 further defining some of these.

The examiner commented that, in view of the fact that some of the amino acids are undefined, there is insufficient guidance in the specification to the skilled person as to how to determine which sequences would act as an antagonist. Applicants do not agree with this. The specification provides ample instruction as to how to go about site-directed mutagenesis procedures (which are, in any case, common knowledge to the skilled person) and the assays to be carried out for determining whether a sequence acts as an antagonist to a ligand for ICAM-4. As noted above, although the required work might be time-consuming, it does not require inventive skill in view of applicants' specification. In relation to claim 27 and new claim 39, the critical amino acids required to be present are specified and, in relation to claim 28 and new claim 40, the full amino acid sequence of a suitable antagonist is set out. The skilled person is, therefore, fully provided by the specification with the means to work the invention and the written description requirements are met.

The examiner's comments in the first paragraph of page 4 of the Office Action are moot in view of the amendment of the claims to refer to antagonists having specific structural features. In addition, new claims 38 and 41 have been added to define the integrins mentioned in the claims, in the event that the examiner considers such a limitation to be necessary.

In relation to the examiner's comments in section 8 of the Office Action, applicants submit that the claims now do refer to an antagonist having specific structural features. At least two examples of antagonists having specific structural features are provided in the specification (SEQ ID NOs: 9 & 10, for example), along with a clear disclosure of the method of how these were identified and how it was shown that they did, indeed, act as antagonists of a ligand of ICAM-4. Therefore, the skilled person would readily be able to identify other peptides which would act as such antagonists in view of the applicants' specification. The skilled person is provided with at least two amino acid sequences and a clear indication of which amino acid residues within these sequences are important for binding. The skilled person could readily vary the other amino acids within a sequence and, using the experiments set out in the specification, determine whether the antagonist activity remained. Therefore, the invention is fully enabled to the skilled person in view of the applicants' specification.

Finally, further evidence of the efficacy of the specific sequences disclosed in the specification is provided in Kaul *et al.* This work utilized a rat model of erythrocyte adhesion to the endothelium, which showed that incubation of erythrocytes with amino acid sequences containing either the FWV or ATSR motifs inhibited adhesion of erythrocytes to the endothelium (see Figure 1 on page C925 and Figure 2 on page C926). It is noted that the amino acid sequences used in this work were one amino acid shorter than either SEQ ID NO:9 or SEQ ID NO:10, as disclosed in the specification. Therefore, this provides further evidence that the skilled person, in view of the specification, was able to determine suitable antagonists, and that the applicants are entitled the scope of protection provided by the present claims. That is, the skilled person can ascertain what does and does not "*materially* affect the *basic* and *novel* characteristic(s) of a composition." *See In re Herz*, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original).

In view of the above clarifications and amendments, applicants request withdrawal of the enablement/written description rejection.

Anticipation Rejection:

On pages 5-7 of the Office Action, the examiner maintains the rejection of claims 25-27 under 35 U.S.C. 102, allegedly as being anticipated by Hermand *et al.*

On page 7 of the Office Action, the examiner also maintains the rejection of claims 25-27 under 35 U.S.C. 102, allegedly as being anticipated by Bailly *et al.* as evidenced by the Provisional Application No. 60/423,391 at page 1.

Applicants respectfully disagree with the examiner and submit that none of the cited references disclose each and every element of the amended claims 26-28, which are directed to an antagonist consisting essentially of 3 to 9 amino acid residues of the A or G strands of ICAM-4, or of an antagonist which is a peptide having the specific amino acid sequence SEQ ID NO:9 or SEQ ID NO:10. In this context, applicant refers the examiner to the dictates of the MPEP that:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Hermand *et al.* does not disclose an antagonist consisting essentially of 3 to 9 amino acid residues of the A or G strands of ICAM-4, or of an antagonist which is a peptide having the specific amino acid sequence SEQ ID NO:9 or SEQ ID NO:10.

Hermand *et al.* discloses a full-length ICAM-4, for example, a 10 amino acid sequence which is included within in that large protein is indicated by the first arrow of Figure 1. This is not a disclosure of an antagonist consisting essentially of the recited number of amino acids. In addition, the amino acid sequence indicated by this arrow does not include an FWV motif. The paragraph "Reagents and antibodies" on page 26003 of Hermand *et al.* refers to an antibody raised against the N-terminal 15 amino acids of ICAM-4. Therefore, Hermand *et al.* does not anticipate the claimed invention.

In order to assist the examiner in further distinguishing the claimed invention from

Hermand *et al.*, applicants submit that there is no disclosure at all in Hermand *et al.* of small fragments of ICAM-4 being functional as antagonists to a ligand for ICAM-4. As the applicants have argued previously, Hermand *et al.* provides a disclosure of the full length sequence of ICAM-4 and an analysis of its structure, setting out the various immunoglobulin folds included in that structure. The skilled person is provided with no teaching or suggestion that isolation of smaller fragments of this sequence would provide an antagonist to a ligand for this sequence. Accordingly, Hermand *et al.* cannot anticipate the claimed invention.

Regarding Bailly *et al.* applicants refer to above clarifications that claim 26 has been amended for clarity. Amended claim 26 is directed to an antagonist that consists essentially of three, four, six, seven, eight or nine amino acid residues of strand A or G of domain 1 of ICAM-4. Thus, the disclosure of Bailly *et al.*, as referred by the examiner, as disclosed in Table 1 as "Peptide 3", does not teach or suggest the claimed invention. Accordingly, Bailly *et al.* does not disclose each and every element of the amended claim 26. The cited provisional application no. 60/423,391 on the other hand, does not rectify the deficiencies of Bailly *et al.* Accordingly, the claimed invention is not anticipated by Bailly *et al.* in combination with the disclosure at page 1 of the provisional application.

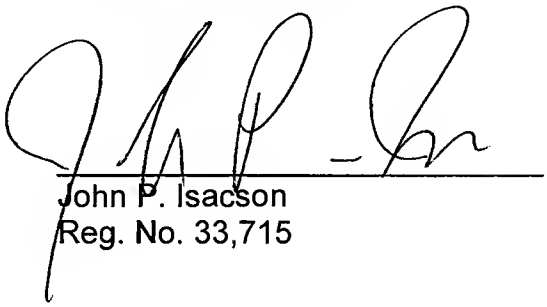
In order to assist the examiner further distinguishing the claimed invention from Bailly *et al.*, applicants submit that in relation to Bailly *et al.*, Table 1 sets out sequences identified using tryptic digestion, presumably of the full length protein. The examiner perhaps takes this disclosure of the sequence of a small fragment of ICAM-4 as an incentive to the skilled person to attempt to isolate such fragments for use as antagonists of a ligand to ICAM-4. It should be noted, however, that Bailly *et al.* represents early (1994) work in the procedure of elucidating the sequence and structure of ICAM-4. The use of tryptic digestion is a means of providing small fragments of a protein, which may then be fully sequenced, the information from each fragment being combined to provide information of the sequence of the whole protein. There is even no suggestion in this disclosure that these short peptides would bind to a ligand of ICAM-4. Accordingly, Bailly *et al.* can not anticipate the claimed invention.

In view of the above clarifications, arguments and amendments, applicants submit that the cited references do not anticipate the claimed invention. Withdrawal of the anticipation rejection is therefore solicited.

REQUEST

Applicants submit that claims 26-28 and 38-43 are in condition for allowance, and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 416-6800 should there be any questions.

Respectfully submitted,



November 7, 2008
Date

John P. Isacson
Reg. No. 33,715

PROSKAUER ROSE LLP
1001 Pennsylvania Avenue, NW
Suite 400 South
Washington, DC 20004
Phone: 202-416-6800
Fax: 202-416-6899
Customer No. 61263